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A Prospective Randomized Trial of Prevention Measures in Patients at High Risk for Contrast Nephropathy

Results of the P.R.I.N.C.E. Study

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OBJECTIVES This study was done to test the hypothesis that a forced diuresis with maintenance of intravascular volume after contrast exposure would reduce the rate of contrast-induced renal injury.

BACKGROUND We have previously shown a graded relationship with the degree of postprocedure renal failure and the probability of in-hospital death in patients undergoing percutaneous coronary intervention. Earlier studies of singular prevention strategies (atrial natriuretic factor, loop diuretics, dopamine, mannitol) have shown no clear benefit across a spectrum of patients at risk.

METHODS A prospective, randomized, controlled, single-blind trial was conducted where 98 participants were randomized to forced diuresis with intravenous crystalloid, furosemide, mannitol (if pulmonary capillary wedge pressure <20 mm Hg), and low-dose dopamine (n = 43) versus intravenous crystalloid and matching placebos (n = 55).

RESULTS The groups were similar with respect to baseline serum creatinine (2.44 ± 0.80 and 2.55 ± 0.91 mg/dl), age, weight, diabetic status, left ventricular function, degree of prehydration, contrast volume and ionicity, and extent of peripheral vascular disease. The forced diuresis resulted in higher urine flow rate (163.26 ± 54.47 vs. 122.57 ± 54.27 ml/h) over the 24 h after contrast exposure ($p = 0.001$). Two participants in the experimental arm versus five in the control arm required dialysis, with all seven cases having measured flow rates <145 ml/h in the 24 h after the procedure. The mean individual change in serum creatinine at 48 h, the primary end point, was 0.48 ± 0.86 versus 0.51 ± 0.87, in the experimental and control arms, respectively, $p = 0.87$. There were no differences in the rates of renal failure across six definitions of renal failure by intent-to-treat analysis. However, in all participants combined, the rise in serum creatinine was related to the degree of induced diuresis after controlling for baseline renal function, $r = -0.36$, $p = 0.005$. The rates of renal failure in those with urine flow rates greater than 150 ml/h in the postprocedure period were significantly lower, 8/37 (21.6%) versus 28/61 (45.9%), $p = 0.03$.

CONCLUSIONS Forced diuresis with intravenous crystalloid, furosemide, and mannitol if hemodynamics permit, beginning at the start of angiography provides a modest benefit against contrast-induced nephropathy provided a high urine flow rate can be achieved. (J Am Coll Cardiol 1999;33:403–11) © 1999 by the American College of Cardiology

Radiocontrast-induced nephropathy, despite attempts to prevent or alter its incidence, has been a significant cause of iatrogenic renal dysfunction contributing to morbidity, prolonged hospitalizations, mortality, and increased costs of health care over the past several decades as the number of radiographic procedures have increased (1). Previous investigations regarding anticipation of this complication have been largely retrospective and uncontrolled (2–4). Trials in humans of prophylactic measures have evaluated hydration strategies, furosemide, mannitol, calcium-channel blockers and, most recently, atrial natriuretic peptide (5–10). Soloman and co-workers (5) showed in a randomized trial that precontrast saline hydration was more effective than saline plus furosemide or mannitol in preventing a rise in postprocedure serum creatinine. This trial, however, did not

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control for the intravascular volume status of the patient before and after the contrast exposure, leaving uncertainty with respect to the optimal hydration and diuresis program for those individuals as high risk undergoing contrast exposure.

The Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation (P.R.I.N.C.E.) study was a randomized, prospective, controlled study of participants with renal dysfunction, which was designed to test the hypothesis that forced diuresis with maintenance of intravascular volume would result in less contrast-induced renal injury.

METHODS

Participants. All patients scheduled for elective coronary angiography, with or without intervention, were screened daily by reviewing the standard, preangiography serum creatinine values and pertinent case histories. Three thousand consecutive patients scheduled for coronary angiography or intervention were screened. Patients with a baseline serum creatinine greater than 1.8 mg/dl were asked to participate, and 100 consented and were enrolled in the study protocol. Exclusion criteria included acute myocardial infarction requiring primary or rescue coronary intervention, use of vasopressors prior to the procedure, cardiogenic shock, current peritoneal or hemodialysis, planned postcontrast dialysis, or allergies to the study medications.

Random assignment. Randomization was carried out with computer-generated random numbers kept in opaque, sealed envelopes. After obtaining written, informed consent, participants were randomized to either experimental or control group based on the assignment found in the numbered envelope in the corresponding participant entry packet. Those participants randomized to the experimental arm were further designated to receive mannitol based on the hemodynamic data that were obtained via Swan-Ganz catheterization. If the pulmonary capillary wedge pressure was less than 20 mm Hg, then mannitol was included in the preventive strategy as described below. The preangiography hydration orders and choice of contrast agent were left to the discretion of the attending physician. All participants were allowed nothing by mouth at least 6 h prior to the procedure, with the exception of oral medications, including diuretics, which were continued.

Treatment protocol. The study protocol was approved by the Human Investigations Committee of William Beaumont Hospital, a 929-bed tertiary-care center. Once informed consent was obtained and randomization completed, an indwelling urinary catheter was placed with urometry for accurate measurement of urine output and routine urinalysis was performed. Prior to performing angiography, all participants underwent right heart catheterization via femoral venous approach. Right atrial, right ventricular, pulmonary artery, and pulmonary capillary wedge pressures were measured and recorded immediately before and after contrast administration. Cardiac output and cardiac index were calculated using the Fick method.

Participants randomized to the control arm received intravenous (IV) crystalloid alone (0.45 normal saline) at 150 ml/h beginning upon arrival to the catheterization laboratory and which was continued during the procedure. Those in the experimental arm received the same IV crystalloid, furosemide as a single dose (1 mg/kg up to a maximum of 100 mg), and IV dopamine (3 mcg/kg/min), upon arrival at the catheterization laboratory and which was continued during the procedure (11,12). Once right heart catheterization was complete, mannitol 12.5 g in 250 ml of 5% dextrose was infused over 2 h if the pulmonary capillary wedge pressure was less than 20 mm Hg. All infusions were given via peripheral IV sites. All intraprocedural events such as hypotension or pulmonary edema were documented on standardized data-collection forms prospectively through the hospital stay by trained research assistants.

After the procedure, all participants received 0.45 normal saline intravenously at a rate of 150 ml/h for 6 h, followed by hourly adjustment in the infusion rate to match the prior hour's urine output. The latter was recorded by nursing staff on the bedside flow sheet. Participants were assessed hourly for hypotension or signs of congestive heart failure. Eight participants received additional diuretics after angiography for treatment of volume overload. Serum creatinine and electrolytes were measured at 12, 24 and 48 h after contrast exposure. If a participant was discharged to home by the attending physician prior to obtaining the 48-h specimen, he or she had phlebotomy performed by an outpatient visiting nurse. Urinary catheters were removed 24 h after the procedure.

Predefined end points. Because varying end points have been used in previous studies, we recorded renal outcomes in six different ways according to the change in serum creatinine and need for renal dialysis. The purpose of this reporting is to allow for comparisons to prior studies and aid in systematic review.

Statistical analysis. Sample size estimates called for a minimum of 44 participants in the experimental and control arms and were based on a standardized effect size of 0.60 (expected effect size of interest being an absolute difference of 0.3 mg/dl in serum creatinine at 48 h divided by an expected SD of 0.5 based on previous literature), $\beta = .20$, power = 80%, and $\alpha = 0.05$ (5). Baseline characteristics are reported in means ± SD or proportions as appropriate. Comparisons were made among continuous variables using analysis of variance (ANOVA) for independent samples, repeated-measures ANOVA for paired samples (change in serum creatinine), or the Kruskal-Wallis H test. Chi-square or the Fisher exact test was used for discrete variables. All hypothesis testing was two-tailed. Relative risks are reported with 95% confidence intervals (CI). Simple linear regression was used for the evaluation of two continuous variables and generation of the Pearson correlation coefficient and its 95%

Table 1. Baseline Characteristics of the Study Sample

	IVF + Furosemide + Dopamine + Mannitol (n = 22)	IVF + Furosemide + Dopamine (n = 21)	IVF Alone (control) (n = 55)	p-Value
Baseline Clinical Characteristics				
Age in years	72.3 ± 5.7	67.0 ± 11.6	69.6 ± 10.7	0.48
Male:Female	17:5	15:6	31:21	–
Prior myocardial infarction	14 (63.6%)	14 (66.7%)	31 (56.4%)	0.54
Hypertension	18 (81.8%)	17 (81.0%)	50 (90.9%)	0.38
Congestive heart failure	8 (36.4%)	9 (42.9%)	28 (50.9%)	0.48
Diabetes	10 (45.5%)	11 (52.4%)	31 (56.4%)	0.69
Peripheral vascular disease	9 (40.9%)	6 (28.6%)	22 (40.0%)	0.61
Abdominal aortic aneurysm	1 (4.6%)	1 (4.8%)	3 (5.5%)	0.98
Prior contrast exposure	18 (81.8%)	11 (52.4%)	34 (61.8%)	0.10
Ejection fraction %	43.6 ± 12.0	39.6 ± 11.8	42.5 ± 13.7	0.66
Medications				
ACE inhibitors	9 (40.9%)	11 (52.4%)	32 (58.2%)	0.39
Calcium channel blockers	13 (59.1%)	10 (47.6%)	28 (50.9%)	0.78
Diuretics	10 (45.5%)	13 (61.9%)	44 (80.0%)	0.01
Beta-blockers	11 (50.0%)	8 (38.1%)	24 (43.6%)	0.80
Insulin	6 (27.3%)	6 (28.6%)	23 (41.8%)	0.39
Oral hypoglycemics	4 (25.5%)	1 (4.8%)	8 (14.6%)	0.37
NSAIDS	4 (25.5%)	6 (28.6%)	14 (25.5%)	0.66
Baseline Lab Measures				
Creatinine (mg/dl)*	2.20 ± 0.38	2.65 ± 1.04	2.55 ± 0.91	0.44
Blood urea nitrogen (BUN) (mg/dl)†	36.00 ± 8.70	48.20 ± 18.06	44.26 ± 15.41	0.05
BUN/Cr ratio	16.54 ± 3.87	19.68 ± 8.08	18.16 ± 5.89	0.61
Estimated CrCl (ml/min)	33.73 ± 10.00	31.44 ± 12.00	30.48 ± 12.95	0.57
Na (meq/L)	138.82 ± 2.58	136.35 ± 4.16	137.56 ± 4.19	0.12
K (meq/L)	4.38 ± 0.53	4.52 ± 0.52	4.47 ± 0.59	0.70
Glucose (mg/dl)‡	140.24 ± 49.55	182.95 ± 104.93	159.46 ± 80.74	0.65
Uric Acid (mg/dl)§	8.38 ± 2.16	9.42 ± 2.84	8.52 ± 2.78	0.48
Hemoglobin (g/dl)¶	11.72 ± 1.63	11.60 ± 1.71	11.04 ± 1.84	0.33
Hematocrit %	34.61 ± 4.93	33.19 ± 6.04	32.51 ± 5.29	0.36
Urine specificity gravity	1.012 ± 0.005	1.013 ± 0.006	1.014 ± 0.009	0.51

*To convert from mg/dl to μmol/liter, multiply by 88.4. †To convert from mg/dl to mmol/liter, multiply by 0.357. Estimated Creatinine Clearance: CrCl = [140 − Age (yrs) × weight (kg)/serum creatinine (mg/dl) × 72]. $CrCl_{Male} = 1 \times CrCl$, $CrCl_{Female} = 0.85 \times CrCl$. ‡To convert from mg/dl to mmol/liter, multiply by 0.05551. §To convert from mg/dl to μmol/liter, multiply by 60.0. ¶To convert from g/dl to mmol/liter, multiply by 0.6167.
IVF = intravenous fluid hydration.

CI. Multivariate techniques including multiple regression, multiple ANOVA, and analysis of covariance (ANCOVA) were used for the evaluation of a continuous outcome variable with respect to multiple independent variables and covariates. Regression coefficients are given ± SE of the estimate. For all tests, the α level of 0.05 was chosen for significance.

RESULTS

Baseline characteristics. One hundred participants were recruited for the study; however, two were withdrawn owing to physician request or a change in clinical status. One participant's procedure was cancelled at the outset of protocol initiation and the other participant was withdrawn shortly after consent and never received study medications.

Baseline characteristics are reported in Table 1. The two divisions of the experimental group and the control group were similar with respect to age, presence of diabetes and other comorbidities, and ejection fraction. The experimental group had a lower rate of regular diuretic use, 53.4% versus 80.0%, respectively, p = 0.01. Baseline laboratory measures were similar among the groups. Procedural factors are reported in Table 2. The overall mean time of being kept without oral fluids prior to contrast exposure was 11.5 ± 0.3 h. During this period, participants received a mean volume of 419.6 ± 22.6 ml in prehydration IV fluids. As dictated by the protocol, those participants who had initial pulmonary capillary wedge pressures ≥20 mm Hg did not receive mannitol. Eight participants (42.9%) of this subset had a prior history of heart failure, and the mean pulmonary capillary wedge pressure was 27.6 ± 13.6 mm Hg compared to 12.1 ± 3.4 and 19.4 ± 12.6 mm Hg in the other experimental subset (furosemide, dopamine, mannitol) and control groups, respectively, p = 0.0002. This subset had a

Table 2. Procedural Factors

	IVF + Furosemide + Dopamine + Mannitol (n = 22)	IVF + Furosemide + Dopamine (n = 21)	IVF Alone (control) (n = 55)	p-Value
Hydration Status				
Hours kept NPO*	11.4 ± 2.8	10.9 ± 3.0	11.7 ± 3.0	0.61
Prehydration infusion volume (ml)	419.8 ± 230.0	350.6 ± 199.9	442.6 ± 219.1	0.31
Initial Hemodynamics				
Mean right atrial pressure (mm Hg)	6.7 ± 3.4	8.8 ± 7.0	7.33 ± 7.0	0.56
Pulmonary artery systolic pressure (mm Hg)	34.0 ± 10.9	49.3 ± 18.4	39.9 ± 16.4	0.008
Pulmonary artery diastolic pressure (mm Hg)	19.9 ± 6.8	29.5 ± 14.1	24.8 ± 11.2	0.03
Pulmonary capillary wedge pressure (mm Hg)	12.1 ± 3.4	27.6 ± 13.6	19.4 ± 12.6	0.0002
Cardiac output (l/min)	5.7 ± 1.9	5.1 ± 1.3	5.1 ± 1.7	0.54
Cardiac index (l/min/m^2)	3.0 ± 0.9	2.7 ± 0.7	2.7 ± 0.6	0.40
Contrast Factors				
Contrast volume (ml)	193 ± 115.1	136.9 ± 69.5	161.5 ± 83.2	0.12
Diatrizoate (Hypaque®)	7 (31.8%)	2 (9.5%)	17 (30.9%)	0.11
Ioxaglate meglumine (Hexabrix®)	15 (68.2%)	19 (90.5%)	38 (69.1%)	0.03
Hemodynamics After Contrast Exposure				
Mean right atrial pressure (mm Hg)	6.4 ± 4.5	8.7 ± 2.0	7.5 ± 4.8	0.63
Pulmonary artery systolic pressure (mm Hg)	36.3 ± 15.3	47.9 ± 16.2	43.4 ± 18.8	0.19
Pulmonary artery diastolic pressure (mm Hg)	22.6 ± 10.8	30.8 ± 11.1	29.1 ± 11.0	0.10
Pulmonary capillary wedge pressure (mm Hg)	14.4 ± 6.6	32.8 ± 12.2	23.2 ± 13.5	0.00004

*NPO = no oral fluids permitted. IVF = intravenous fluid hydration.

greater use of low-ionic contrast chosen by the operator, 90.5% versus 68.2% and 69.1%, respectively, p = 0.03. In addition, the operators tended to use less contrast in this group, 136.9 ± 69.5 ml versus 170.5 ± 93.5 ml for all others, p = 0.16.

Intent-to-treat analysis. Results with respect to renal and clinical outcomes are given in Tables 3 and 4. Table 3 reports results stratified by the two experimental subsets and the control group. The experimental subset receiving mannitol had the greatest diuresis in the first 8 h, 2343.2 ± 1051.8 versus 1786.8 ± 731.7 and 1368.1 ± 704.7 ml of urine in the furosemide and dopamine subset and control groups, respectively, p = 0.00003. Urine flow rates for the first 24 h postcatheterization tracked in a similar fashion, 167.6 ± 58.0, 158.7 ± 51.6, and 122.6 ± 54.3 ml/h, respectively, p = 0.003. The mean individual change in serum creatinine at 48 h, the primary end point, was 0.48 ± 0.86 versus 0.51 ± 0.87 in the experimental and control arms, respectively, p = 0.87. Primary end points for the experimental subgroups and control group are displayed in Figure 1.

Specific renal outcomes are given in Table 4 with the experimental arm subsets combined for the intent-to-treat analysis by randomized allocation. The relative risks for the experimental group ranged between 0.43 and 1.05 with five of the six definitions favoring the experimental arm. All of these measures, however, were not statistically significant (Table 4). Two participants in the experimental arm and five participants in the control arm required dialysis during the days after contrast exposure. All seven of these participants had measured urine flow rates <145 ml/h (57th percentile of flow) during the first 24 h after contrast exposure.

Levels of diuresis and outcomes. The relationship between induced urine flow rate in the first 24 h and change in serum creatinine in the first 48 h after contrast exposure was evaluated using a quintile analysis as shown in Figure 2. Greater increases in serum creatinine were observed in the lowest quintiles of flow. We used a cutoff for urine flow rate of 150 ml/h in the first 24 h after the procedure (the same as the baseline IV infusion rate input during that time frame) and report renal outcomes for the six definitions of renal failure in Figure 3. Using the aggregate end point, the rates of renal failure in participants with urine flow rates greater than 150 ml/h in the postprocedure period were significantly lower, 8/37 (21.6%) versus 28/61 (45.9%), p = 0.03.

A negative correlation existed between urine flow and change in serum creatinine, r = −0.35 (95% CI −0.53 to −0.14) p = 0.001, when all participants were combined. Multiple linear regression was used to control for the baseline creatinine clearance, and the overall regression was significant (multiple R = 0.36, p = 0.005; baseline creatinine clearance, β = 0.10 ± 0.11, p = 0.36; urine flow rate, β = −0.36 ± 0.11, p = 0.001) with the relationship between induced urine flow rate and resultant serum creatinine being independent of the baseline renal function (Fig. 4).

Low-ionic versus high-ionic contrast. The choice of contrast agent was left up to the operating physician. The mean change in serum creatinine, 0.46 ± 0.77 and 0.58 ± 1.05, p = 0.54, was similar for those who received

Table 3. Comprehensive Results

	IVF + Furosemide + Dopamine + Mannitol (n = 22)	IVF + Furosemide + Dopamine (n = 21)	IVF Alone (Control) (n = 55)	p-Value
Serum Creatinine (Cr) (mg/dl)*				
Baseline	2.20 ± 0.38	2.69 ± 1.04	2.55 ± 0.91	0.14
After 12 h	2.32 ± 0.59	2.65 ± 1.09	2.61 ± 0.88	0.37
After 24 h	2.56 ± 0.79	2.69 ± 1.12	2.69 ± 0.98	0.86
After 48 h	2.72 ± 1.19	3.21 ± 1.28	3.08 ± 1.20	0.45
Mean individual change	0.56 ± 1.02	0.40 ± 0.69	0.51 ± 0.87	0.21
Urine Output (ml)				
0 to 8 h	2343.2 ± 1051.8	1786.8 ± 731.7	1368.1 ± 704.7	0.00003
9 to 16 h	885.9 ± 413.0	1165.2 ± 599.5	788.2 ± 571.2	0.03
17 to 24 h	700.6 ± 467.0	948.5 ± 610.4	725.1 ± 432.0	0.17
IV input/urine output ratio 0 to 8 h	0.82 ± 0.59	1.05 ± 0.52	1.64 ± 2.55	0.02
IV input/urine output ratio 9 to 16 h	1.35 ± 0.73	0.99 ± 0.38	1.55 ± 1.15	0.11
IV input/urine output ratio 17 to 24 h	2.38 ± 5.00	1.33 ± 1.78	1.16 ± 0.67	0.64
IV input/urine output ratio 0 to 24 h	0.91 ± 0.34	0.87 ± 0.29	1.30 ± 0.87	0.02
Urine flow rate (ml/h)	167.62 ± 58.03	158.69 ± 51.57	122.57 ± 54.27	0.003
Renal Failure Outcomes by Definition				
>25% rise in Cr	7 (31.8%)	7 (33.3%)	17 (30.9%)	0.98
>50% rise in Cr	3 (13.6%)	1 (4.8%)	8 (14.5%)	0.50
>100% rise in Cr	1 (4.5%)	0 (0.0%)	2 (3.6%)	0.64
>1.0 mg/dl rise in Cr	3 (13.6%)	3 (14.3%)	8 (14.5%)	0.99
Cr > 5.0 mg/dl or dialysis	2 (9.1%)	3 (14.3%)	10 (18.2%)	0.60
Any of above	7 (31.8%)	8 (38.1%)	21 (38.2%)	0.86
Clinical Outcomes				
Dialysis	1 (4.5%)	1 (4.8%)	5 (9.1%)	0.73
Developed CHF	0 (0.0%)	2 (9.5%)	5 (9.1%)	0.16
Transient hypotension	0 (0.0%)	1 (4.8%)	3 (5.5%)	0.35
VT/VF	0 (0.0%)	0 (0.0%)	1 (1.8%)	0.56
Required IABP	0 (0.0%)	2 (9.5%)	3 (5.5%)	0.22
Death	1 (4.5%)	0 (0.0%)	1 (1.8%)	0.49
LOS (h)	52.7 ± 68.3	78.4 ± 121.9	39.2 ± 54.3	0.18

*To convert from mg/dl to μmol/liter, multiply by 88.4.
IVF = intravenous fluid hydration; IV = intravenous; CHF = congestive heart failure; VT/VT = ventricular fibrillation and or ventricular tachycardia; IABP = intraaortic balloon pump; LOS = length of stay.

low-ionic (n = 76) and high-ionic contrast (n = 22), respectively. Multivariate analysis, which took into account the baseline estimated creatinine clearance, randomization arm, contrast volume, and diabetes, did not find a significant independent effect of the type of contrast used on the primary outcome nor was an interaction found between contrast type and randomization arm.

Diabetics. The overall proportion of diabetics was 52/98 (53.1%) in the study. The breakdown of proportions across treatment groups is given in Table 1. The mean individual change in serum creatinine was 0.62 ± 0.86 versus 0.34 ± 0.84 mg/dl for diabetics and nondiabetics, respectively, p = 0.11. Multivariate analysis, which took into account the baseline-estimated creatinine clearance, randomization arm, contrast volume and type, did not find a significant inde-

Table 4. Specific Renal Outcomes by Intent-to-Treat, Experimental Arm Versus IV Hydration Alone (Control) Arm

Renal Outcome	Experimental Arm (n = 43)	IVF Alone (control) Arm (n = 55)	Relative Risk (95% CI)	p-Value
>25% rise in Cr*	14 (32.6%)	17 (30.9%)	1.05 (0.59–1.89)	0.96
>50% rise in Cr	4 (9.3%)	8 (14.5%)	0.64 (0.21–1.98)	0.54
>100% rise in Cr	1 (2.3%)	3 (4.4%)	0.43 (0.05–3.96)	0.63
>1.0 mg/dl rise in Cr	6 (14.0%)	8 (14.5%)	0.96 (0.36–2.56)	0.83
Cr >5.0 mg/dl or dialysis	5 (11.6%)	10 (18.2%)	0.64 (0.24–1.73)	0.37
Any of above	15 (34.9%)	21 (38.2%)	0.91 (0.54–1.55)	0.90

*To convert from mg/dl to μmol/liter, multiply by 88.4.
IVF = intravenous fluid hydration.

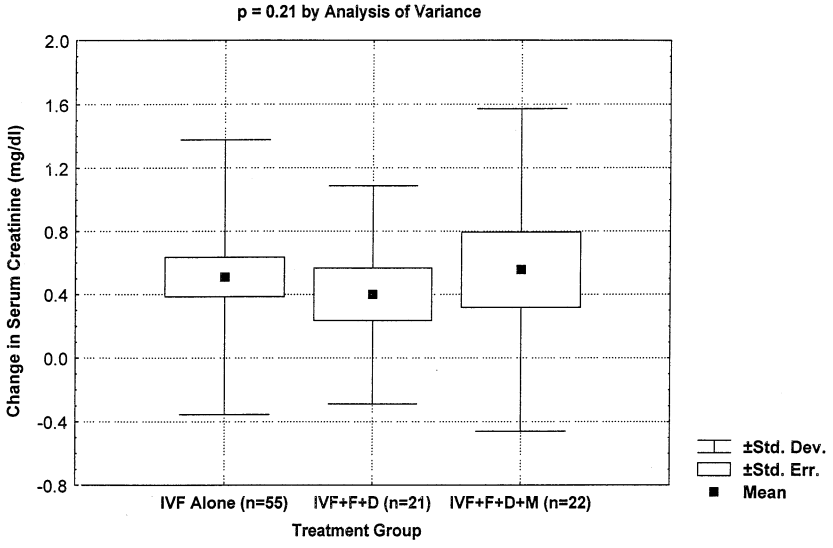

Figure 1. Mean individual change in serum creatinine at 48 h in the control group and the two subsets of the experimental group. IVF = intravenous 0.45 normal saline at 150 ml/h for 6 h with upward adjustment for urine flow rates greater than 150 ml/h (control group). F = furosemide 1 mg/kg intravenously up to 100 mg at the start of the procedure. D = intravenous dopamine 3 mcg/kg/min at the start of the procedure and continued for 6 h. M = mannitol 12.5 g in 250 ml of 5% dextrose infused at the start of the procedure over a 2-h period. p = 0.21 by analysis of variance.

pendent effect of diabetes after adjustment for multiple comparisons, p = 0.19. In addition, no interaction was seen between diabetes and the treatment arms (p = 0.81 for the interaction term).

Effects of mannitol. The study design allowed for an individual evaluation of mannitol as a protective agent. Despite a more favorable clinical profile with a lower baseline creatinine (2.20 ± 0.38 vs. 2.59 ± 0.94 for all others, p = 0.05) and lower right-sided heart pressures (Table 2), the mannitol-treated subset had similar resultant serum creatinine measures, 2.72 ± 1.19 versus 3.11 ± 1.21 mean, p = 0.22, and 0.61 ± 0.98 versus 0.58 ± 0.72 mg/dl increase, p = 0.88. One of the seven participants who required dialysis was in the mannitol-treated subset.

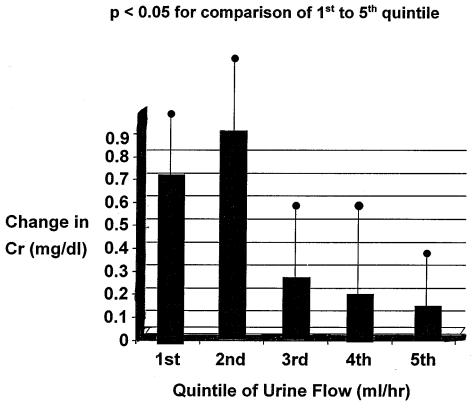

Figure 2. Change in postcontrast exposure serum creatinine at 48 h stratified by measured urine flow rate, n = 98 (to convert from mg/dl to μmol/liter, multiply by 88.4). p < 0.05 for comparison of 1st to 5th quintile.

Complications. Two participants had major intraprocedural complications, with major defined as hypotension (systolic blood pressure less than 80 mm Hg) for at least 2 min, ventricular tachycardia or fibrillation, worsened or new congestive heart failure, or hemodynamic instability requiring intraaortic balloon pump placement. Two participants expired during the study period, one due to massive intracranial hemorrhage and the other from cardiac failure after a prolonged arrest during coronary intervention.

DISCUSSION

This study has demonstrated that the induction of a forced diuresis while attempting to hold the intravascular volume in a constant state with replacement of urinary losses provides a modest protective benefit against contrast-induced renal injury, which is independent of baseline renal function. This is particularly true if mean urine flow rates were above 150 ml/h. We used the split-treatment arm design to evaluate the additive effect of mannitol as a protective agent and found this agent appeared to offer no additional benefit to loop diuretics and low-dose dopamine.

Rates of renal failure. We found the overall rate of renal failure of 31.6% (defined as a rise in serum creatinine greater than 25% above the baseline) to be considerably greater than the general population rate of 14.5% described in our large epidemiologic study (2). This can be attributed to a greater degree of baseline risk in study participants with the mean serum creatinine being 2.50 ± 0.86 versus 1.3 ± 0.4 in the

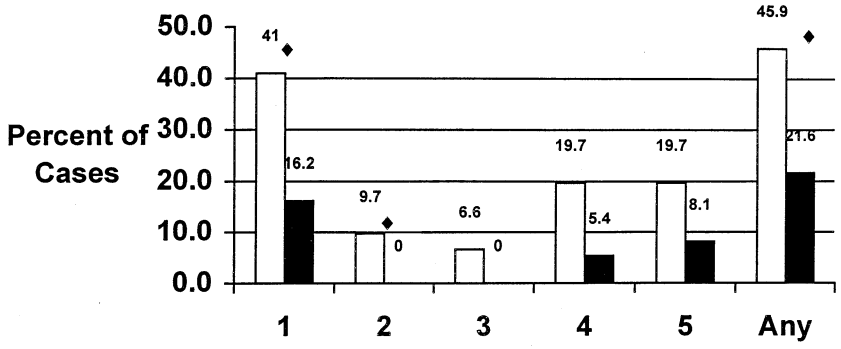

Figure 3. Rates of renal failure shown by multiple definitions of the end point stratified over the cutpoint of 150 ml/h of urine flow induced by a forced diuresis, n = 98. □ = Low UFR (≦150 ml/h); ■ = High UFR (>150 ml/h). ◆p < 0.05. 1 indicates >25% rise in serum creatinine; 2 indicates >50% rise in serum creatinine; 3 indicates >100% rise in serum creatinine; 4 indicates >1.0 mg/dl rise in serum creatinine; 5 indicates a peak creatinine of >5.0 mg/dl at 48 h or dialysis. UFR = urine flow rate.

general population undergoing coronary intervention (2). However, our observed rate of renal failure in those participants with high urine flow rates (16.2%) was much lower than the similarly defined rates described by Weisberg and co-workers (9), who reported rates in a comparable population (baseline creatinine 2.5 ± 0.1, 48% diabetics) for the following singular treatment arms: saline 40%, dopamine 33%, atrial natriuretic peptide 50%, and mannitol 30%. This difference in outcomes is most likely due to the replacement of urinary losses with additional IV hydration carried out in our study, which highlights the need for maintaining intravascular volume in preventing contrast-induced renal injury.

A previous study by Solomon and co-workers (5) showed that diuresis with mannitol or furosemide without adjusted intravascular volume replacement was of no benefit. The study provided no hemodynamic stratification and allowed for diuretic-induced prerenal volume reduction, which likely masked any observed benefit in terms of postprocedure serum creatinine. The treatment groups in the Solomon study did not combine diuretics with low-dose dopamine and thus cannot be directly compared to the experimental arm in our trial (5).

Effects of mannitol. Our findings with respect to the lack of additive benefit of mannitol are consistent with two prior studies including the randomized trial by Solomon (5,13). However, three prior studies in humans with more severe degrees of baseline renal dysfunction have shown a modest benefit from mannitol infusion (6,9,14). All of these studies were uncontrolled and only one was published in manu-

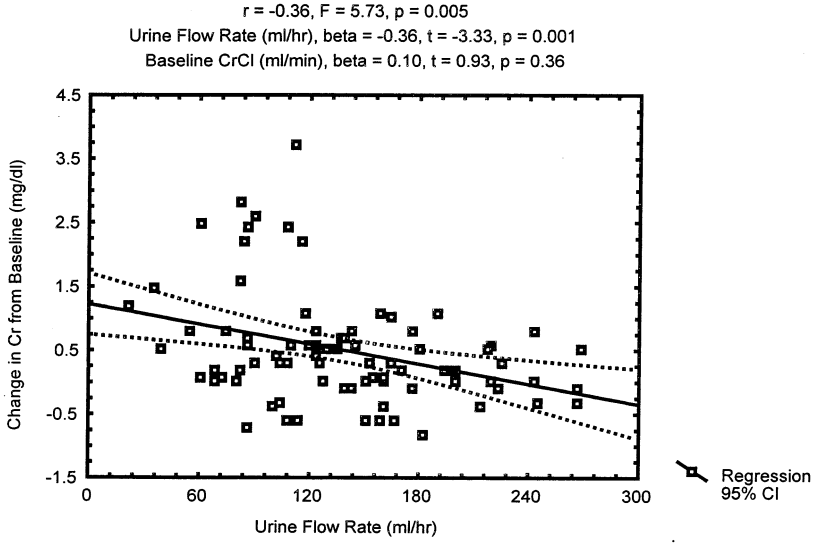

Figure 4. Regression of induced urine flow rate predicting resultant change in serum creatinine from baseline to that measured at 48 h in mg/dl, controlling for baseline renal function (to convert from mg/dl to μmol/liter, multiply by 88.4). This shows a relation between increasing urine flow rates in the first 24 h after contrast exposure and reduction in renal injury measured at 48 h that is independent of baseline renal function in all 98 aggregated participants, r = −0.36; F = 5.73; p = 0.005. Urine flow rate (ml/h), beta = −0.36; t = −3.33; p = 0.001. Baseline CrCl (ml/min), beta = 0.10; t = 0.93; p = 0.36.

script form. We have shown that mannitol induces an increase in urine flow rate above that caused by furosemide and dopamine. Although no statistically significant difference was shown in the resultant increases in mean serum creatinine, we found only one participant in the mannitol-treated subset versus six in the other subsets who went on to require dialysis. The mannitol-treated subset, however, had more favorable hemodynamic profiles with lower pulmonary capillary wedge pressures by the nature of the study design; hence, it may have had a baseline hemodynamic advantage over the other groups.

Importance of preventive strategies. We and others have shown that the most important factors predicting contrast nephropathy are baseline renal function, presence of diabetes, and the contrast volume received (2,15–17). Serious renal failure after contrast exposure can be predicted in the majority of individuals at risk (2,15). Therefore, a preventive strategy even with a small degree of efficacy, can be targeted for beneficial outcomes. This is important because renal failure requiring dialysis after coronary intervention is associated with poor outcomes, including a 40% in-hospital mortality and 19% 2-year survival (2). These outcomes are consistent with in-hospital mortality rates associated with new-onset dialysis after bypass surgery and in the intensive-care-unit setting (1,4,18). Our study indicates that a forced diuresis appears to reduce the baseline risk of preexisting renal dysfunction within the range of creatinine clearance observed in our participants (range 10.2 to 64.6 ml/min). A target urine flow rate of greater than 150 ml/h in the first 24 h after the contrast exposure was related to a 52.9% relative reduction in the rate renal failure using the aggregate end point.

The P.R.I.N.C.E. study employed the principle of forced diuresis to preserve renal function as has been described in other toxic nephropathies such as rhabdomyolysis (19,20). Suggested mechanisms of action supporting this concept include limiting the contrast-nephron exposure time, maintenance of renal blood flow and limiting hypoxic injury after contrast-induced, endothelin-mediated vasoconstriction, and acceleration of tubule and collecting duct flow with reduced sludging and precipitation of contrast material and tubular cells (21–23).

Study limitations. Limitations of our study include the small sample size, split-experimental arm, and active hydration in the control group, which all worked to limit the effect size and reduce the power of the study. The study design, however, did allow us to make mannitol-specific inferences. In addition, it created a distribution of urine flow rates after the procedure, which allowed for evaluation of benefit by the level of diuresis. Other limitations include the fact that the quantity and type of contrast agent used was left up to the operator, and hence, was uncontrolled. Although the contrast dose was similar between the experimental and control arms, 166.0 ± 98.2 versus 161.5 ± 83.2 ml, $p = 0.80$, low ionic contrast tended to be used more often in the experimental arm, 34/43 (79.1%) versus 34/55 (61.8%), $p = 0.07$. Our multivariate analysis, however, did not indicate significant confounding due to contrast type. Finally, detailed assessments of the postcontrast urine were not undertaken. Measures of specific gravity and degree of cast formation may have shed light on mechanisms of benefit attributable to this strategy.

Conclusions. In conclusion, we have shown that a systematic protocol of forced diuresis with diuretics and low-dose IV dopamine, in patients at high risk for contrast nephropathy, can increase postprocedure urine flow rates causing less renal injury after the contrast exposure. A urine flow rate greater than 150 ml in the first 24 h after contrast exposure is related to a modest reduction in the rates of acute renal failure.

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